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Pedunculopontine arousal system physiology – Deep brain stimulation (DBS)

Edgar Garcia-Rill[a,*], *Brennon Luster*[a], *Stasia D'Onofrio*[a], *Susan Mahaffey*[a], *Veronica Bisagno*[b], *Francisco J. Urbano*[b]

[a]*Center for Translational Neuroscience, University of Arkansas for Medical Sciences, Little Rock, AR, USA*
[b]*IFIBYNE-CONICET and ININFA-CONICET, University of Buenos Aires, Argentina*

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ABSTRACT

This review describes the wake/sleep symptoms present in Parkinson's disease, and the role of the pedunculopontine nucleus in these symptoms. The physiology of PPN cells is important not only because it is a major element of the reticular activating system, but also because it is a novel target for deep brain stimulation in the treatment of gait and postural deficits in Parkinson's disease. A greater understanding of the physiology of the target nuclei within the brainstem and basal ganglia, amassed over the past decades, has enabled increasingly better patient outcomes from deep brain stimulation for movement disorders.

1. Introduction

There are now over 200 Parkinson's disease (PD) patients worldwide implanted with stimulating electrodes in the region of the pedunculopontine nucleus (PPN), which is part of the reticular activating system (RAS) [1]. This review will describe the wake/sleep dysregulation present in PD, and the rationale for using PPN DBS, which is not based on its modulation of arousal but rather on its influence on gait and posture. We will briefly consider the early research demonstrating the role of the PPN in posture and locomotion. It is becoming clear that the parameters of stimulation found to be salutary for the treatment of PD are those that match the intrinsic properties of PPN neurons. It is worth noting that stimulation of the region of the PPN dates to the earliest

Abbreviations: DBS, deep brain stimulation; EEG, electroencephalogram; LC, locus coeruleus; PD, Parkinson's disease; PGO, ponto-geniculo-occipital; PPN, pedunculopontine nucleus; REM, rapid eye movement; RAS, reticular activating system; SN, substantia nigra; STN, subthalamic nucleus; SubCD, subcoeruleus nucleus dorsalis

*Correspondence to: Center for Translational Neuroscience, Department of Neurobiology and Developmental Sciences, University of Arkansas for Medical Sciences, Slot 847, 4301 West Markham St., Little Rock, AR 72205, USA. Tel.: +1 501 686 5167; fax: +1 501 526 7928.
E-mail address: GarciaRillEdgar@uams.edu (E. Garcia-Rill).

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studies on the RAS, and we will contrast PPN stimulation with activation of other wake/sleep related areas. Finally, we will propose a number of measures to help identify possible effects of PPN DBS on the arousal system. Although PPN DBS has virtually no negative effects or reported adverse events, its clinical application needs further investigation. While most PPN DBS studies focus on movement, few address changes in wake/sleep regulation.

2. Sleep and arousal in Parkinson's disease (PD)

PD is characterized by a variety of symptoms, which include 3–7 Hz resting tremor, rigidity, postural and gait abnormalities, akinesia, and bradykinesia [1]. In addition, a number of other symptoms are present, including abnormal reflexes as well as higher-level impairments in frontal lobe function and cognition. Although many of the symptoms are manifested after a degenerative process has reduced the function of dopaminergic substantia nigra (SN) neurons below a certain threshold, there are a number of additional degenerative or functional changes in such areas as the locus coeruleus, raphe nuclei, basal forebrain, and frontal cortex [2]. More recently, it has been found that the degenerative process begins in the glossopharyngeal, vagal, and olfactory nerve nuclei, accounting for non-motor symptoms [3]. The process ascends from these brainstem regions to involve the SN and ultimately the cortex. PD patients also manifest decreased habituation of the blink and other reflexes [4–8], and exhibit anxiety disorder (including panic attacks) and depression [9–13]. Moreover, cognitive impairments related to attentional deficits are present [14–17], and these correlate with decreased frontal lobe glucose utilization [15,18–22].

PD patients show sleep disturbances that include disturbed rapid eye movement (REM) sleep drive (specifically the presence of REM sleep during both night and day, along with hallucinations) [23], which may be related to disease severity [Wetter], decreased slow wave sleep (SWS), frequent awakenings leading to daytime sleepiness, and insomnia [24–26]. Disrupted sleep and early morning awakenings are the most common insomnia symptoms, but PD patients do not appear to have difficulty initiating sleep [27]. Nevertheless, the most frequent sleep disorder in PD patients was insomnia in over 80% of those tested [28]. The reader is referred to a recent review on PPN and insomnia [29]. Another recent review describes sleep changes observed in animal models of PD [30]. These observations suggest that the reticular activating system (RAS), especially the pedunculopontine nucleus (PPN) that is in charge of waking and REM sleep, is overactive in PD. We carried out a study of the P50 midlatency auditory evoked potential, which is generated by PPN projections to the intralaminar thalamus in the human [31]. The P50 potential is a click stimulus-induced midlatency auditory evoked response (at a 50–70 ms latency) that follows the brainstem auditory evoked potentials that occur at <10 ms latency, and the primary auditory evoked "Pa" response at a 25 ms latency. The P50 potential is as follows: (a) sleep state-dependent, such that it is present during waking and REM sleep, but not during SWS, e.g. it is manifested during arousal states when PPN is active, (b) blocked by low doses of scopolamine, e.g. it is generated by cholinergic projections of the PPN, and (c) rapidly habituating, e.g. reticular in origin with low synaptic security [31]. Animal studies showed that lesions of the PPN or injections of inhibitory agents into the PPN eliminated the equivalent vertex-recorded potential (P13 in the rodent, "wave a" in the feline), emphasizing the origin of the waveform as the PPN [31]. In summary, the P50 potential is an arousal-related waveform in the human.

We showed that the amplitude of the first P50 potential response of a pair of stimuli administered 250 ms apart was 40% higher in PD patients [32]. This suggests an increase in arousal to phasic stimuli in this disease. Moreover, P50 potential habituation (the amplitude of the second response as a percent of the first response of a pair) decreased significantly in the PD group as a whole. In addition, there was a statistically significant decrease in habituation with severity. This suggests a deficit in sensory gating in the disorder. We also measured the P50 potential in PD patients who received bilateral pallidotomy that alleviated their motor symptoms, and found that the amplitude and habituation of the P50 potential was within normal levels [33]. Fig. 1 (left side) shows the effects of PD on the habituation of the P50 potential as the disorder advances from stages 3 to 4. The percent habituation at the 250 ms and 500 ms interstimulus intervals in age- and gender-matched controls was similar to patients at stage 3, but they both differed from patients in stage 4 at the 250 ms interstimulus interval, and from those in stage 5 at both the 250 ms and 500 ms intervals. That is, the sensory gating deficit increased with clinical stage.

Fig. 1 (Right side) shows that the percent habituation in stage 5 patients differed from controls at the 250 ms and 500 ms intervals, but was restored to control levels by bilateral pallidotomy. We speculated that the increased PPN output in PD was instantly re-inhibited or down regulated by the surgery to normalize sensory gating and hyperarousal to phasic inputs [33]. The importance of these results is that there is an immediate effect by the therapy in reinstituting a balance of activity. The damage to the SN apparently induces a disturbance that can be corrected by additional damage (pallidotomy) [33]. One conclusion is that the symptoms involved can be alleviated almost instantly by appropriate treatment, not requiring extended reorganization or regeneration, etc. Since lesion of a region provides little flexibility in the approach, a therapeutic strategy that can be modified with changes in status, for instance, as the disease progresses, would be more desirable.

Prior to the use of L-DOPA for the treatment of PD, lesions of the thalamus and pallidum were being used, but pharmacological treatment became the preferred form of therapy [34]. While the use of L-DOPA has been effective for some of the symptoms of the disease, long-term use (>5 years) and increasing dosages can lead to dyskinesias. Other agents have been used but they provide less effective relief and can produce unwanted side effects. Surgical treatment includes the use of thalamotomy, pallidotomy, and subthalamic nucleus lesions. Nowadays, the most common therapeutic approach involves deep brain stimulation (DBS), with the most common site used being the subthalamic nucleus (STN). However, DBS of the PPN is now being used for the treatment of PD.

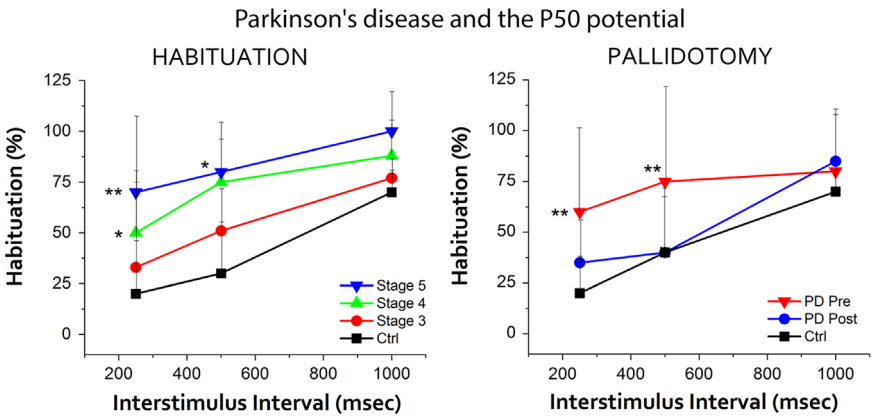

Fig. 1 – The P50 potential in PD. Left. Paired click stimuli were delivered at three interstimulus intervals (ISI), 250 ms, 500 ms, and 1000 ms, so that a recovery curve could be plotted. Age- and gender-matched control subjects (black squares) showed ~20%, 30%, and 60% habituation of the second response, respectively. PD patients at stage 3 (red circles) showed ~30%, 50%, and 75% habituation, correspondingly, and were not different from controls. Stage 4 patients showed ~50%, 75%, and 80% correspondingly, and differed from controls at the 250 msec ISI. Stage 5 patients showed decreased habituation at ~73%, 76%, and 95%, correspondingly. Stage 5 patients differed significantly from control subjects at the 250 ms ($p<0.01$), and 500 ms (*$p<0.05$) ISIs (Data from [32]). Right. PD patients recorded before bilateral pallidotomy (inverted red triangles) showed habituation at ~60%, 75%, and 80%, respectively for the three ISIs. After pallidotomy (blue circles), the same patients showed ~35%, 35%, and 60%, respectively. The percent habituation differed significantly between the post- and pre-surgery results at the 250 ms and 500 ms ISIs (**$p<0.01$), and were not different from control subjects (black squares) (Data from [33]).**

3. Stimulation of the region of the pedunculopontine nucleus (PPN)

The first investigators to stimulate the region of the PPN were Moruzzi and Magoun [35] to transform the electroencephalogram (EEG) from slow wave activity to fast activity. They used chloralose-anesthetized or midbrain-transected (decerebrate) cats and stimulated the region of the mesencephalic reticular formation. They also performed lesions immediately anterior to the PPN that eliminated the effects of such stimulation. These studies typically used stimulation frequencies of 300 Hz, but established that 50 Hz stimulation was close to the lowest effective frequency. Interestingly, the effects of stimulation had a latency, typically under 1 s, that is, stimulation was not instantaneous, but effective in inducing high frequency EEG at short latency.

Many years later, other investigators reported the presence of a region called the mesencephalic locomotor region (MLR), stimulation of which in the midbrain-transected (decebrate) cat, induced controlled locomotion on a moving treadmill [36]. By controlled locomotion, workers meant that increasing current levels elicited a walk, then a trot, then a gallop. Moreover, locomotion entailed alternation of antagonists in the same limb, and of agonizts in different limbs. These parameters are important because they establish a specific relation to stepping, rather than a general correlation with so-called "activity" or "exploration". The parameters of stimulation were quite specific, requiring low current levels (<100 μA), 40–60 Hz stimulation, and localized to the lateral, but not the medial, cuneiform nucleus. We investigated this region and ultimately established that the MLR was not a locomotion-specific region, but actually a rhythmogenic area that overlapped with the histologically identified PPN, that basically drove descending projections to induce changes in posture and locomotion [37–39]. Stimulation at high frequency (300 Hz) typically induced reduction in extensor muscle tone [40], while stimulation at 40–60 Hz induced locomotion [37–39]. We concluded that the optimal site of stimulation was in the lateral cuneiform nucleus, and that stimulation "recruited", rather than "induced" locomotion, since it required ~1 s of stimulation to have the desired effect [37–39,41]. It was this line of research that led us to propose the use of PPN DBS for the treatment of PD.

A recent review considers in detail the reasons why these parameters are effective for inducing stepping [1], but will not be considered here. Briefly, beta/gamma oscillations in every PPN cell are mediated by high threshold, voltage-dependent N- and P/Q-type calcium channels [42]. We discovered that every cell in the PPN manifests beta/gamma frequency oscillations when depolarized using current ramps, but not when using current steps [42]. This is the only property shared by every PPN neuron, whether cholinergic, glutamatergic, or GABAergic. That is, ramping up current avoided the activation of potassium channels that would prevent the membrane from reaching the depolarized levels needed to activate the high threshold, voltage-dependent N- and P/Q-type calcium channels essential to beta/gamma frequency oscillations [42]. This property makes it necessary that PPN cells be ramped up to reach the depolarizing thresholds for voltage-dependent calcium channels that are typically located in the dendrites [43]. Fig. 2 illustrates the properties of PPN cells that require that stimuli be ramped up, instead of suddenly turned on, in order to induce intrinsic gamma band oscillations. Current steps failed to maintain depolarization of the membrane potential, probably due to potassium channel activation, while ramps slowly (~1 s) depolarize the membrane potential to activate the high threshold calcium channels.

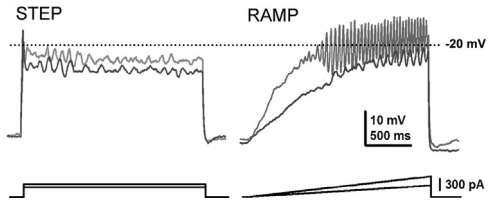

Fig. 2 – Manifestation of gamma oscillations in PPN neurons requires current ramps instead of current steps. Left. Patch clamp recordings from a PPN neuron in the presence of synaptic blockers and TTX to record intrinsic membrane properties. Application of current steps could not maintain the membrane potential at highly depolarized levels, preventing beta/gamma oscillations mediated by high threshold calcium channels to be manifested. Right. Application of current ramps slowly depolarized the membrane potential until reaching the threshold of the calcium channels mediating the oscillations. The window of activation for this cell was in the −30 mV (black record) to −20 mV (gray record) (Data from [42]).

4. The role of the RAS in posture and locomotion

The RAS is a phylogenetically conserved system that modulates fight-or-flight responses. During waking, man's ability to detect predator or prey is essential to survival. Under these circumstances, it is not surprising that the RAS can modulate muscle tone and locomotion. This system is thus intrinsically linked to the control of the motor system in order to optimize attack or escape. During REM sleep, the atonia keeps us from acting out our dreams. In fact, only our diaphragm and eye muscles appear to be acting out dream content. Therefore, during both waking and REM sleep, two states modulated by the PPN, the RAS can influence muscle tone and locomotion via the same reticulospinal systems [44]. For example, in a standing individual, there is tonic activation of anti-gravity, mainly extensor, muscles (the same ones inhibited in the atonia of REM sleep). Before the first step can be taken, there must be flexion of the leg, therefore, there must be a release from standing, or extensor inhibition, from this postural extensor bias. It should be noted that the first sign of stepping from a standing position will always be extensor inhibition to unlock the knees, only then followed by flexion. Extensor inhibition is thus the first action modulated by descending PPN outputs. The question is whether or not the extensor inhibition is prolonged to induce postural collapse (as in the cataplexy of narcolepsy), or does it lead to flexion–extension alternation and locomotion [44].

Outputs from the PPN and perhaps its descending target, the SubCoeruleus nucleus dorsali (SubCD), activate reticulospinal systems that lead to profound hyperpolarization of motoneurons, which is the mechanism responsible for the atonia of REM sleep [45]. Cholinergic projections from the PPN to the medioventral medulla elicit locomotion [46]. Outputs from this medullary region in turn activate reticulospinal systems that lead to the triggering of spinal pattern generators to induce stepping [37,38,47]. In general, electrical stimulation of the pontine and medullary reticular formation is known to induce decreased muscle tone at some sites, while producing stepping movements at other sites. This suggests the presence of a heterogeneous, distributed system of reticulospinal motor control. The required parameters of stimulation for eliciting these differing effects are important such that instantaneous, high frequency (>100 Hz) trains (similar to high frequency bursting activity in the range of ponto-geniculo-occipital (PGO) burst neurons that may drive the atonia of REM sleep) trigger pathways which lead to decreased muscle tone, while lower frequency (40–60 Hz) tonic stimulation leads gradually to the "recruitment" of locomotor movements [38,41]. Therefore, given the extensive evidence, it is to be expected that the PPN, as part of the RAS, should modulate both posture and locomotion in addition to arousal.

5. Stimulation of other regions

The region of the PPN is not the only site stimulated to induce changes in arousal [44]. Regions aside from the RAS implicated in the modulation of waking include: (a) the orexin-containing neurons of the lateral hypothalamus, (b) the cholinergic neurons of the basal forebrain, and (c) the histamine-containing neurons of the tuberomammillary nucleus. However, it is important to note the amount of time that stimulation of these regions takes to induce waking. Why is the latency to induction of a waking EEG important? The implication is that short latency effects on waking reflect more direct activation of the cortical EEG, whereas long latency effects reflect a circuitous route for achieving high frequency EEG activity in the cortex. Typically, stimulation of the RAS, either in the region of the PPN using electrodes [35,47], or optogenetic methods activating the locus coeruleus [48], will induce high frequency arousal-related EEG changes within 1–2 s. However, stimulation of the basal forebrain induces high frequency EEG but only after 15 s of stimulation [49], and stimulation of the lateral hypothalamus, or optogenetically activated orexin neurons, elicits high frequency EEG activity only after 20 s of stimulation [48]. The fact is that stimulation of the RAS-thalamic pathway elicits cortical arousal ten times faster than stimulation of the basal forebrain or lateral hypothalamic/orexin pathways. That is, both the basal forebrain and hypothalamus need to project elsewhere to induce a waking EEG, and, as we will see below, neither region is the final common pathway for arousal.

a. *Orexin lateral hypothalamic neurons* – Some of the sleep disturbances manifested in PD may be due to loss of hypocretin cells in this disorder [50]. While much attention has been paid to hypothalamic neurons in the control of waking, de Lecea's lab has optogenetically engineered animals that have rhodopsin cation channels in orexin and in noradrenergic locus coeruleus (LC) neurons [51]. Their findings showed that light activation of orexin neurons shows a latency ~20 s to induce waking, implying that its output must travel elsewhere before the animal awakens. When they light activated LC cells, the animals woke up immediately, within 1–2 s, but if LC was inactivated by introduction of chloride channels, orexin neuron stimulation failed to awaken the animals. These results suggest that orexin neurons must first affect at least one of their

descending RAS targets, the LC, in order to manifest a waking effect *in vivo*. That is, the lateral hypothalamic system may act through the RAS to elicit arousal.

The prolonged latency required to induce arousal after orexin neuron activation suggests that this region "recruits" waking but only after prolonged latency. The result showing that optogenetic inactivation/inhibition of the LC in advance of activation of optogenetically altered orexin neurons fails to induce waking [52] suggest that, in the absence of ascending RAS, specifically the LC, orexin cells cannot induce a waking-like EEG. In other words, descending projections to the RAS may be essential for these cells to ultimately produce an effect on waking. Moreover, the role of these neurons is regulated by sleep deprivation. Optogenetic stimulation experiments found that sleep deprivation blocks the ability of orexin to activate its downstream targets and enhance waking [53], suggesting that these neurons can be kept from exercising an effect on waking by simple sleep deprivation. Therefore, rather than a specific role in arousal, orexin neurons have been implicated in the integration of motor, metabolic, circadian, and limbic inputs that can influence sleep to wake transitions [54].

b. *Basal forebrain neurons*- Activation of the basal forebrain induces low amplitude, high frequency EEG in the cortex [55]. Recordings in this region showed that most cells were related to waking and very few related to slow wave sleep (SWS) [56]. Later studies found that basal forebrain neurons did indeed fire in relation to both waking and REM sleep [57]. In addition, lesions of basal forebrain neurons were found to increase SWS [58]. All of these findings suggest that basal forebrain cells help manifest the high frequency cortical EEG. However, a number of groups have suggested that this cell group modulates waking via projections to the brainstem [59–62], and perhaps, also via the thalamus [62,63]. This suggestion is supported by experiments in which stimulation of mesopontine cholinergic nuclei in the brainstem resulted in cortical activation, an effect that persisted even after lesions of the basal forebrain [64].

Moreover, early studies showed that acute precollicular transections in which the basal forebrain was anterior to the transection, eliminate fast activity related to waking and REM sleep, i.e. the basal forebrain by itself cannot drive the cortex to maintain gamma band activity *in vivo* [35,65]. This was confirmed by studies in which transection at the level of the posterior edge of the inferior colliculus to the anterior hypothalamus, thus disconnecting the basal forebrain and cortex from the brainstem induced profound coma [65]. Despite the fact that chronic transections did suggest that the basal forebrain modulates waking to some extent, the RAS appears to be the final common pathway for induction of the high EEG frequency states of waking and REM sleep by the basal forebrain.

c. *Histamine tuberomammillary neurons*- The histamine neurons of the tuberomammillary nucleus represent the only histaminergic cells in the brain. They are located in the posterior hypothalamus and they have a reciprocal relationship with ventrolateral preoptic cells [59,60]. Tuberomammillary cells are inhibited by ventrolateral preoptic cells that promote sleep [66], and are excited by orexin cells of the lateral hypothalamus [67]. However, tuberomammillary histamine neurons do not manifest pronounced changes in activity in relation to high frequency EEG [68]. Moreover, knockout animals lacking the histamine synthesizing enzyme histidine decarboxylase do not show major changes in cortical EEG and waking time [69,70]. These authors proposed that the tuberomammillary system is more related to waking in novel environments, suggesting a modified role in arousal. These findings collectively imply that the tuberomammillary system is also not a final common pathway for arousal.

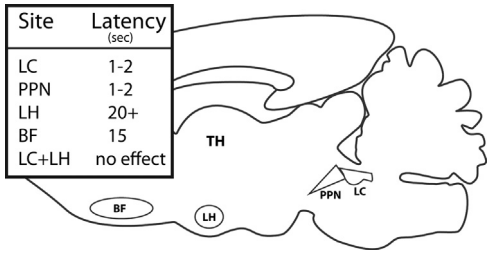

Fig. 3 – Short latency arousal following RAS stimulation compared to long latency after basal forebrain or hypothalamus stimulation. Sagittal diagram of the rodent brain shows the locations of the basal forebrain (BF), lateral hypothalamus (LH), locus coeruleus (LC), pedunculopontine nucleus (PPN), and thalamus (TH). Stimulation of the LC showed a 1–2 s latency to waking, while stimulation of the mesencephalic reticular formation near the PPN showed a similar latency. However, stimulation of the LH exhibited a 20+ s latency, while stimulation of the BF showed a 15 s latency. Inhibition of the LC showed that stimulation of the LH was ineffective, suggesting that LH orexin neurons must activate the RAS in order to have an effect on waking (Data from [44]).

Fig. 3 outlines the locations of the PPN, locus coeruleus (LC), lateral hypothalamus, and basal forebrain. Stimulation of the PPN and LC using electrodes or optogenetic methods induces arousal or high frequency EEG within 1–2 s. However, stimulation of the lateral hypothalamus or basal forebrain typically takes 10–20 times longer, and inactivation of the LC prevents lateral hypothalamus stimulation from inducing arousal. Basically, while the lateral hypothalamus, basal forebrain, and tuberomammillary systems modulate waking, they are not primary drivers of arousal.

6. PPN deep brain stimulation (DBS)

DBS for the treatment of basal ganglia disorders is most often used in the subthalamic region and internal pallidum, but these will not be addressed here. As far as PPN DBS is concerned, early studies focused on PD patients who presented with axial symptoms and gait disturbances [71], with subsequent studies using increasingly sophisticated localization and visualization methods [72–74]. Most patients showed improvements in gait using stimulation at 15 and 25 Hz [75], while stimulation at 50 and 70 Hz showed improvements in falls [76]. Sleep patterns were improved by stimulation at 10 and 25 Hz [77,78], while sleep

scores and executive function were improved by stimulation at 25 Hz [79]. Double-blind studies established that bilateral stimulation was better than unilateral stimulation at 20–35 Hz in improving reaction time, fall scores, and gait [80,81]. Presumably, the continuous stimulation used during DBS helps maintain beta/gamma band activity in the PPN, but does not produce hyperarousal because the system is characteristically rapidly habituating. That is, the phasic function of the RAS is not amplified. That may be why continuous PPN DBS does not produce undesirable arousal side effects, and may in fact help stabilize PPN output. Thus, it is possible that continuous PPN DBS provides a persistent signal, regulating and stabilizing the circuits at physiological (gamma band) frequencies [1]. This helps maintain waking and awareness, thereby also improving the tonic function of the RAS. It would be interesting to determine if PPN stimulation at 40–60 Hz could be used to upregulate PPN output to restore arousal levels in disorders such as coma or reduced alertness. It should also be noted that PPN DBS could be used to downregulate PPN output if so desired, perhaps by applying higher frequencies such as 100 Hz or higher. It would also be interesting to determine if continuous high frequency stimulation could be used to decrease hyperarousal, or alleviate symptoms of excessive arousal. The P50 potential, as a measure of level of arousal and sensory gating, could be used to determine the effects of DBS, and if such treatment corrects any increases in amplitude or decreases in habituation.

Interestingly, DBS in the medial or intralaminar thalamus is being used with great success for the treatment of Tourette's syndrome [82,83]. One side effect of intralaminar thalamus DBS for Tourette's syndrome is profound fatigue. The parameters of stimulation typically include 24 h stimulation at high frequencies (>100 Hz). This side effect may respond to decreased frequency of stimulation (e.g. 40–60 Hz) and for 20/24 h schedules (Visser-Vandewalle, personal communication). That is, stimulation at frequencies and schedules closer to those used for PPN DBS may help prevent the fatigue manifested.

7. Conclusion

While the use of PPN DBS is becoming more common, there is still much testing to be performed before it can become clinical routine. However, the foregoing should make it evident that optimal outcomes may ensue from using stimulation parameters that take advantage of novel information on the physiology of PPN cells. That is, stimulation at the natural frequency of PPN cells (20–60 Hz) is likely to recruit beta/gamma band intrinsic membrane oscillations that are maintained by the continuous application of PPN DBS. Both ascending arousal and descending motor control projections from the PPN are thus optimally activated to normalize PPN outputs. In the implementation of PPN DBS, we should determine its effects on wake/sleep cycles by performing sleep studies before and after implantation. One study performed sleep measures and found that PPN DBS improved not only nighttime sleep, but also daytime sleepiness [84]. If PPN DBS can normalize wake/sleep characteristics, then the technique can be determined to have a positive outcome on wake/sleep dysregulation in this disorder. In PD patients followed longitudinally, delta and theta power increased while higher frequencies, including gamma, decreased, and these changes correlated with cognitive decline [85]. Determining the effects of PPN DBS on gamma band power, but especially on gamma band maintenance, would be very important for assessing the beneficial effects of PPN stimulation on higher functions. A number of neurological and psychiatric disorders are also characterized by interrupted or decreased gamma band activity [39,44].

There is some information that PPN DBS may improve cognitive function [86], and that low frequency stimulation (5–30 Hz) may improve executive and higher functions [73], but this issue needs further elucidation. Lesions of the PPN disturb attention, executive function and working memory [87], therefore, it should be expected that PPN DBS may beneficially affect higher functions using the appropriate parameters of stimulation. In addition, the PPN has been proposed to participate in the process of preconscious awareness, the mechanism that allows us to evaluate the world around us on a continuous basis [44]. This process is embedded in the formulation of our perceptions and actions, and modulates higher-level beta/gamma processing through its projections to the intralaminar thalamus, basal ganglia, hypothalamus, and basal forebrain. That is why it affects functions as disparate as waking and REM sleep, mood and perception, and homeostatic regulation. The effects of PPN DBS also need to be studied for potential modulation of this essential survival mechanism, preconscious awareness.

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